Recent advances in many areas of reproductive technology, such as intracytoplasmic sperm injection (ICSI) and other forms of assisted fertilization, have been rapid. In many respects, these advances have outstripped our knowledge of the fundamental processes of human and animal sperm–egg interactions at fertilization. One of the major unresolved issues is the identity of the complementary molecules on the sperm surface involved in the early interactions with the extracellular matrix of the egg (the zona pellucida) and this review focuses on this controversial area. Other recent reviews on this topic include: Snell and White (1996), Brewis and Moore (1997), Benoff (1997) and McLeskey et al., (1998). For general reviews on the mammalian sperm acrosome reaction and fertilization, see: Yanagimachi (1994) and Allen and Green (1997).

When the fertilizing spermatozoon reaches the egg (ovum), it must first penetrate the surrounding cumulus mass or oophorus, consisting of follicular cells dispersed in a polymerized hyaluronic acid matrix (Yanagimachi, 1994). In most mammals that have been studied, an acrosome-intact spermatozoon usually makes contact with the egg to undergo a specific gamete recognition process. Gamete recognition is mediated by complementary molecules associated with the extracellular matrix of the oocyte (the zona pellucida) and the plasma membrane over the sperm head. Subsequent to initial (primary) sperm–zona binding, the fertilizing spermatozoon undergoes the acrosome reaction. The acrosome reaction is a major exocytotic event over the entire apical region of the sperm head, characterized by multiple-point fusions between the outer acrosomal membrane and the overlying plasma membrane, which exposes the acrosomal contents of the spermatozoon and its resistant inner acrosomal membrane (Yanagimachi, 1994; Allen and Green, 1997). Acrosomal exocytosis is essential for fertilization and, once acrosome-reacted, the fertilizing spermatozoon undergoes secondary sperm–zona binding before penetration of the zona pellucida (Fig. 1). After passing through the zona, the fertilizing spermatozoon fuses with the egg membrane (oolemma), then enters the egg to enable pronuclear formation and syngamy to occur.

Role of zona pellucida glycoproteins in gamete recognition

The zona pellucida is the extracellular matrix surrounding ovulated mammalian eggs. In most species, including mice and humans, the zona pellucida is composed of three separate glycoproteins: zona pellucida glycoprotein 1 or ZP1 (ZPB), ZP2 (ZPA) and ZP3 (ZPC) (for reviews, see Wassarman, 1995; Albertini and Wassarman, 1994; Wassarman, 1995). The seminal work of Bleil and Wassarman in the early 1980s established that mouse ZP3 serves as both the primary ligand for sperm binding and also as a trigger for the acrosome reaction in the fertilizing spermatozoon (Bleil and Wassarman, 1980; Wassarman, 1995).

Owing to the paucity of eggs available for research, much less is known about the initial events of human sperm–egg recognition. Some groups have attempted to produce recombinant human ZP3 to obviate this problem, but it has proved very difficult to obtain purified biologically active material. However, there are some reports to show that recombinant ZP3

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Gamete recognition: sperm proteins that interact with the egg zona pellucida

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The gamete recognition and initial binding processes that are crucial for the success of mammalian fertilization are mediated by moieties associated with the extracellular matrix of the egg (the zona pellucida) and the head of the fertilizing spermatozoon. The zona proteins involved have been characterized in some detail, with ZP3 and ZP2 generally acknowledged to be responsible for the initial (primary) and secondary interactions, respectively. However, the identity of the complementary molecules on the sperm surface is highly contentious and remains unresolved. This review summarizes the current knowledge and controversies in this research area. The credentials of some of the major candidates and the probability of the involvement of multiple sperm receptors with different binding characteristics are assessed. Resolving this very important gap in our understanding is an essential prerequisite to understanding fully the molecular and signal transduction events that cause sperm acrosomal exocytosis. Such fundamental information is also imperative for the development of novel forms of contraception (or sterilization) targeted against specific sperm epitopes. Moreover, this information may contribute to our understanding of certain types of male infertility.
Fig. 1. Schematic diagram of early mammalian gamete interactions. (a) After passing through the cumulus, the fertilizing spermatozoon reaches and binds to the zona pellucida. (b) Initial (primary) binding of the intact sperm head to the zona pellucida (ZP3) initiates the sperm acrosome reaction (1). The plasma membrane (PM) and outer acrosomal membranes (OAM) undergo multiple point fusions leading to membrane vesiculation (2). Release of the acrosomal contents (3) enables secondary binding between the sperm inner acrosomal membrane and the zona (ZP2). This interaction orientates the thrusting spermatozoon and allows penetration through the zona (4). NM, nuclear membrane.
Table 1. The main candidate sperm proteins that may be involved in primary interactions with the zona pellucida

<table>
<thead>
<tr>
<th>Candidate protein</th>
<th>Species</th>
<th>Type of interaction proposed</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>95 kDa Tyrosine kinase receptor</td>
<td>Mouse</td>
<td>Proposed to act as a receptor tyrosine kinase via protein–protein interactions with ZP3</td>
<td>Leyton and Saling, 1989; Burks et al., 1995</td>
</tr>
<tr>
<td>Zona receptor kinase (ZRK)</td>
<td>Human</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-1,4-Galactosyltransferase (GalTase)</td>
<td>Mouse</td>
<td>Protein component of GalTase interacts with carbohydrate (GlcNAc residues) of ZP3</td>
<td>Miller et al., 1992</td>
</tr>
<tr>
<td>sp56</td>
<td>Mouse</td>
<td>Protein component of sp56 interacts with carbohydrate (galactose residues) of ZP3</td>
<td>Bleil and Wassermann, 1990; Bookbinder et al., 1995</td>
</tr>
<tr>
<td>Spermadhesins*</td>
<td>Pig</td>
<td>Protein component of spermadhesins interacts with carbohydrates of zona</td>
<td>Töpfner-Petersen et al., 1998</td>
</tr>
<tr>
<td>Zonadhesin</td>
<td>Pig</td>
<td>Protein component of zonadhesin has carbohydrate binding domains</td>
<td>Hardy and Garbers, 1994, 1995</td>
</tr>
</tbody>
</table>

This table is not intended to be comprehensive but lists the proteins for which there is strongest evidence for primary zona binding. Please note that some of these candidates have also been characterized less well in other species.

* A family of several different proteins.

will induce the sperm acrosome reaction (van Duin et al., 1994; Brewis et al., 1998). This finding has reinforced the view that ZP3 is also the main physiological inducer of the human sperm acrosome reaction and, in most other species studied, ZP3 homologues are also implicated as the key primary binding molecules (Yanagimachi, 1994).

Induction of the sperm acrosome reaction as a result of sperm–ZP3 interaction causes the release of the sperm acrosomal contents and allows for a secondary phase of sperm–zona interaction which is thought to involve a more persistent binding with the inner acrosomal membrane. This secondary binding of the spermatozoon to the zona is poorly understood but, in mice, ZP2 has been identified as the major egg protein responsible for this interaction (Bleil et al., 1988; Yanagimachi, 1994). Secondary binding has not been studied in any detail in humans, although there is some evidence to suggest that ZP2 is also involved (Hinsch et al., 1998).

**Sperm proteins involved in primary interactions with ZP3**

Although ZP3 is generally accepted to be the main egg protein involved in initial (primary) sperm–zona binding in most species, the identification of the complementary egg receptor on the surface of mammalian spermatozoon has proved more elusive. There are important reasons why research progress has been so problematic. Sperm–zona interactions are functionally complex and probably involve several different sperm proteins. One of the greatest obstacles has been the paucity of zonae material available for research purposes, and this is especially the case in humans. Research groups engaged in this area have perhaps been guilty at times of studying the problem too subjectively, using approaches that focus only on their favoured protein. It is also relatively difficult to purify proteins biochemically from mammalian spermatozoon as it is difficult to obtain sufficient material, and proteins are also easily degraded during purification by acrosomal proteases. Importantly, it has proved very difficult to clone genes, as spermatozoon have little, if any, functional mRNA, and so testis gene expression and cloning must be used. This technique needs to be used with caution as the fertilizing spermatozoon undergoes considerable modification after it leaves the testis during sperm maturation to enable it to achieve fertilizing potential.

Despite much research over the past decade, the identity of the key sperm protein involved remains controversial, with a number of candidate proteins proposed that may bind to ZP3 and trigger the acrosome reaction. A list of the best characterized candidates, together with the types of interaction believed to be involved, are presented (Table 1). On the basis of current evidence, β-1,4-galactosyltransferase and the 95 kDa tyrosine kinase receptor are the strongest candidates but even in these cases concerns persist with regard to aspects of their credentials.

**The 95 kDa tyrosine kinase receptor**

The 95 kDa tyrosine kinase receptor was first characterized in mice and has been shown to be phosphorylated in response to zona protein and to bind ZP3 directly (Leyton and Saling, 1989). In humans, a monoclonal antibody (mAb 97.25) has been shown to inhibit sperm–zona binding and immunoprecipitation experiments revealed that this antibody recognized a 95 kDa phosphotyrosine-containing protein (Moore et al., 1987; Burks et al., 1995). A dual cloning strategy using the mAb 97.25 and anti-phosphotyrosine monoclonal antibodies was used subsequently to identify the cDNA (hu9 clone) encoding a novel human 95 kDa sperm tyrosine kinase receptor, named the zona receptor kinase (ZRK), and is presumed to be similar to the mouse protein (Burks et al., 1995). However, there has been much controversy regarding the 95 kDa tyrosine kinase receptor/ZRK. It was reported to be a tyrosine-phosphorylated hexokinase in mice, but this has been disproved (Saling et al., 1995). There is also much uncertainty about the cDNA of human ZRK, as the sequence exhibits close similarity to the proto-oncogene c-mer even though it is more closely related to mouse than to human c-mer (Bork et al., 1996).

In addition, direct binding of ZP3 to the 95 kDa protein has only been shown by Saling’s group, although supporters of this
candidate argue that the data in the mouse system is convincing. The fact that recombinant human ZP3 has also been shown to cause an increase in the tyrosine phosphorylation of a human 95 kDa protein is further evidence that such a moiety is somehow involved in initial gamete recognition (Burks et al., 1995; Brewis et al., 1998). Such zona-induced changes in tyrosine phosphorylation of a 95 kDa have also been demonstrated unequivocally in cats (Pukazhenthi et al., 1996) and hamsters (V. L. Nixon and I. A. Brewis, unpublished). Therefore, it appears that this effect is conserved in mammalian spermatozoa and the 95 kDa protein remains the only human candidate for which there is evidence for interactions with ZP3.

**β-1,4-Galactosyltransferase (GalTase)**

Perhaps the strongest research to date has characterized a mouse β-1,4-galactosyltransferase (GalTase). Galactosyltransferases comprise a group of enzymes involved with the intracellular synthesis of complex carbohydrates in the Golgi apparatus and endoplasmic reticulum (McLeskey et al., 1998). An isoform of GalTase is also present on the surface of mouse spermatozoa over the head region and is believed to form associations in a lectin-like manner by specifically recognizing and binding terminal N-acetylgalactosamine (GlcNAc) residues of ZP3 O-linked oligosaccharides rather than to possess intrinsic enzymatic activity (Miller et al., 1992). Such a result is of importance when considering the work of Florman and Wassarman (1985) who demonstrated that O-linked sugars in mouse ZP3 are specifically recognized by mouse spermatozoa. A drawback of GalTase as a candidate is that it is uncertain whether it is conserved, since its presence in human spermatozoa is controversial (Benoff, 1997). Certainly, there is no direct evidence for interaction with zona proteins and this will have to be examined more fully in the future.

Studies involving the production of transgenic mice have provided important clues regarding the importance of GalTase. Spermatozoa from mice that overexpress a surface GalTase transgene bind more solubilized ZP3 than do spermatozoa from wild-type animals. However, they are less able to bind to intact zonae, indicating that binding requires optimal rather than maximal GalTase expression (Youakim et al., 1994). GalTase-null knockout mice have also been produced by the same workers (Lu and Shur, 1997). Surprisingly, knockout males are fertile even though spermatozoa from these animals are unable to undergo the acrosome reaction in response to ZP3. Hence, the GalTase-activated initiation of the acrosome reaction in these mice appears to be dispensable for fertilization, even though certain events do appear to be less efficient than in the wild-type. This raises the question as to whether GalTase offers some physiological or competitive advantage to spermatozoa, even if its presence is not an absolute requirement for fertilization.

**sp56**

A mouse lectin-like 56 kDa zona oligosaccharide-interacting peripheral membrane protein (sp56), which is a member of a superfamily of protein receptors that includes the α subunits of complement 4B-binding protein, has also been shown to interact directly with ZP3 in cross-linking studies. sp56 is believed to interact with the terminal galactose residues of ZP3 O-linked oligosaccharides and is species-restricted (present in mice and hamsters, absent in guinea-pigs and humans) (Bleil and Wassarman, 1990; Cheng et al., 1994; Bookbinder et al., 1995). However, a protein termed AM67, with almost identical homology to sp56, has been shown to be localized to the acrosomal matrix of guinea-pig spermatozoa rather than to the plasma membrane (Foster et al., 1997). It must now be questioned whether sp56 is involved during initial gamete interaction or, in acrosomal matrix–zona interactions during and after the acrosome reaction.

**Spermadhesins**

Spermadhesins form a novel family of low molecular weight (12–16 kDa) secretory proteins found in the male genital tract. Spermadhesins are major products of seminal plasma and have been characterized most extensively in pigs. In bulls and horses, they associate peripherally with the sperm surface and possess carbohydrate-binding domains. After ejaculation, spermadhesins form a protective coat around the acrosomal region of the sperm head and may prevent premature acrosomal exocytosis. Spermadhesins are believed to act as primary sperm-binding proteins owing to their capacity to interact with both O- and N-linked oligosaccharides and, in addition, they possess heparin-binding activity. However, it has yet to be established whether spermadhesins are involved directly in sperm–zona interaction at the time of fertilization (Töpfer-Petersen et al., 1998).

**Zonadhesin**

Zonadhesin has been characterized in pigs and shown to be similar to blood von Willebrand factor, with repeats that might facilitate multiple interactions with the zona, possibly by carbohydrate binding. This transmembrane protein has been shown to possess high-affinity species-specific binding to zona and is the only candidate sperm protein in which such species specificity has been observed at a molecular level (Hardy and Garbers, 1994, 1995). This finding is particularly interesting since the pig zona contains a distinctive subunit structure and these differences might account for the restricted binding of zonadhesin to pig zonae only (Nakano et al., 1996).

**Other candidate proteins**

Many other proteins have been proposed to interact with the zona pellucida via carbohydrate-binding domains. Indeed, the heavily glycosylated nature of the zona pellucida means that it is a naturally sticky matrix and it is perhaps not surprising that many sperm proteins have been shown to associate with it. Among the best characterized of these proteins are the rabbit sperm autoantigens, such as sp17 (Richardson et al., 1994). The gene for this protein has also been cloned in humans but there is no information about its interaction with human zonae proteins (Lea et al., 1996). Other proposed carbohydrate-binding proteins include: human sperm selectin-like molecules; a guinea-pig fucose receptor; mouse, rat and human α-d-mannosidase; a human mannose receptor; mouse fucosyltransferase; and a rat and human galactose receptor. However, these have been poorly characterized and no direct interaction with zona proteins has been shown. Further description is
beyond the remit of this article but see Benoff (1997) for further details and references.

One final candidate worth mentioning is sulfoglycolipid immobilizing protein 1 (SLIP-1) which is peripherally associated with the plasma membrane over the acrosomal region of mouse spermatozoa. SLIP-1 binds to germ cell-specific glycolipid (sulfogalactosylglycerolipid) on spermatozoa and appears to possess many characteristics of a sperm protein involved in zona binding and, particularly, the early adhesion events (Tanphaichitr et al., 1993). These findings raise the intriguing possibility that glycolipid interactions are also important during sperm–zona interaction, although this hypothesis needs to be investigated further before firm conclusions can be drawn (Moase et al., 1997).

### Sperm proteins involved in secondary interactions with ZP2

As yet, the component of the acrosome-reacted spermatozoon involved in secondary binding with ZP2 remains unidentified. The most likely candidate for a ZP2 receptor in the spermatozoon is proacrosin–acrosin, although the evidence is not conclusive (Brewis and Moore, 1997). Acrosin has a fucose-binding domain and has been shown to interact with the zona pellucida in a number of species but this has not been demonstrated in humans (Töpfer-Petersen and Henschen, 1987). In addition, spermatozoa from mutated mice without the acrosin gene will still penetrate the zona and fertilization occurs (Baba et al., 1994) but there are also studies in humans that indicate that spermatozoa will not penetrate the zona if a trypsin inhibitor is present to inhibit acrosin activity (Liu and Baker, 1993). Some workers have proposed that the sperm hyaluronidase PH-20 is also involved in secondary interactions, but the evidence is not convincing (see Benoff, 1997). In addition, the importance of proteolytic enzymes, such as acrosin, released from the acrosomal contents during sperm penetration of the zona pellucida has been re-evaluated by Bedford (1998), illustrating the importance of continually questioning our understanding of the molecular mechanisms of fertilization.

### The concept of multiple sperm proteins acting in concert

The number and diverse nature of candidate ZP3-binding proteins is perhaps surprising, but most workers in the field recognize that multiple receptors are probably involved and that this is necessary to facilitate the many complex events that occur during sperm–zona binding. Initial sperm–zona adhesion (loose binding), specific tight binding, induction of a signal transduction cascade to initiate the acrosome reaction and secondary binding to facilitate zona penetration all need to be co-ordinated, and there is probably a hierarchy of interactions involving different sperm proteins. The requirement for multiple sperm proteins is also supported by the temporal and spatial differences observed during sperm–zona binding.

Since fertilization is a fundamental process essential for propagation of the species, it might be expected that a number of regulatory processes would have evolved to ensure that initial contact between the spermatozoon and zona leads to fertilization. It is more likely that a combination of binding events takes place, some of which may not be essential, but which optimize the chances of fertilization. There might also be a degree of redundancy involved in what is a crucial process to the individual (Snell and White, 1996).

Thaler and Cardullo (1996a,b) have performed some elegant experiments investigating sperm–zona binding affinities in mice. They have shown that the initial adhesion is a high affinity event but that there are both high and low affinity binding events, indicating the involvement of multiple receptors, and perhaps also multiple ligands, forming a fertilization complex. This notion is also supported by data from our group showing that at least four different human sperm proteins cross-link to ZP3 in vitro (Kiani et al., 1994).

Sperm–zona interactions might occur as either protein–protein, protein–carbohydrate, carbohydrate–carbohydrate interactions or a combination of these binding phenomena. There is evidence from animal studies to indicate that all of these occur and a summary is shown (Fig. 2). It has been proposed that carbohydrate–carbohydrate interactions are important during initial sperm–zona adhesion. After this there are regulated protein–carbohydrate interactions (for example, GalTase)
and protein–protein interactions (for example, the 95 kDa tyrosine kinase receptor), that is, sperm proteins could recognize carbohydrate and protein components of ZP3. In addition, glycolipid interactions may also be important, although to date this has not been demonstrated. Cofactors may also be involved in these events and this may be akin to transmembrane signalling by T-lymphocyte antigen receptors in which complement components bind via oligosaccharides to membrane co-factors to initiate activation of the cell (Brewis and Moore, 1997).

**Sperm–zona adhesion and species specificity**

Primary sperm–zona binding may be classified as cell-extracellular matrix (ECM) adhesion, although the induction of the acrosome reaction by zona proteins is more in keeping with a rapid cell–cell interaction. All of the sperm proteins that have been studied in sufficient detail (with the exception of the 95 kDa protein) have been shown to act by binding carbohydrate components of ZP3 and it has been argued that these sperm proteins are important in the initial sperm–zona adhesion events (Benoff, 1997). These sperm proteins may also confer specificity, as successful sperm–zona binding and fertilization occur in a species-specific manner. However, this is not true in the strictest sense, as sperm–zona interaction and the subsequent events of fertilization can sometimes occur with gametes from very closely related species (Yanagimachi, 1994). Although many consider that species specificity is a function of the sperm or zona carbohydrate epitopes expressed (Benoff, 1997), it is possible that it also involves protein interactions or at least species restriction of certain sperm proteins. Indeed, pig zonadhesin appears to be present only in pigs and does not bind zonae from different species (Hardy and Garbers, 1994). The need for a molecular mechanism to confer species specificity may be another reason for different sperm ZP3-binding proteins (or perhaps certain modifications of the same proteins) in different species.

**Signalling by sperm proteins to initiate the acrosome reaction**

Mammalian fertilization processes have been highly conserved during evolution (Bedford, 1992) and it is our contention that the key recognition and signal transduction events probably involve receptor elements common to all mammalian spermatozoa, and that these are overlaid with species-specific domains or cofactors (Brewis and Moore, 1997). An attraction of the 95 kDa protein is that it does appear to be conserved. GaTase also appears to be conserved, although the evidence in humans is conflicting (Benoff, 1997). The actual molecular signalling mechanisms underlying the sperm acrosome reaction are still very poorly understood and one of the appeals of the 95 kDa tyrosine kinase receptor as a candidate is that it has the characteristics of a classical receptor molecule and is, therefore, intrinsically capable of initiating signal transduction cascades that might lead to the acrosome reaction. There is some limited evidence to support the notion that tyrosine phosphorylation, by activating phospholipase C and phosphoinositide 3-kinase, is important during the acrosome reaction but this has yet to be associated to the 95 kDa protein (Tomes et al., 1996; Fisher et al., 1998). This is an attractive proposition, as phosphoinositide-linked pathways mediate the later stages of the acrosome reaction (McLeskey et al., 1998).

There has been one report in mouse spermatozoa suggesting that aggregation of GaTase may activate a heterotrimeric G-protein complex containing a Gα subunit (Gong et al., 1995). Other lines of evidence indicate that G-proteins, and particularly G-proteins, indirectly regulate the voltage-dependent calcium channels responsible for the zona-induced acrosome reaction (for review, see Kopf et al., 1995). This evidence, and the lack of signalling characteristics in any other candidates, supports further the potential importance of GaTase and the 95 kDa tyrosine kinase receptor. However, the full extent of any multimeric adhesion–signalling complex proteins in the sperm plasma membrane remains to be elucidated.

Although zona proteins are widely believed to be the main physiological inducers of the acrosome reaction, other agonists have been shown to cause acrosomal exocytosis in human spermatozoa in vitro, although their physiological relevance in vivo remains uncertain. The most studied of these agonists include progesterone which, in vivo, may be derived from either the cumulus matrix surrounding the egg or follicular fluid (Osman et al., 1989). Although progesterone has been shown to induce the human sperm acrosome reaction in vitro, this is to a significantly lesser extent than with zona proteins and it is generally held that, in vivo, ZP3 is the main agonist. However, there is some evidence in mice to indicate that progesterone has a priming or synergistic effect on zona-induced acrosomal exocytosis. If this is the case, it presents another level of complexity to the signalling events that trigger the acrosome reaction and will make elucidation of key sperm proteins even more exacting (Roldan et al., 1994).

**Future directions**

Transgenic mice containing chimaeric zonae with mouse ZP1 and ZP2 and human ZP3 have been produced recently. Although ZP3 is generally recognized as the main egg protein involved in initial sperm binding, human spermatozoa failed to bind to the zona. However, mouse spermatozoa not only bound but also successfully fertilized the egg (Rankin et al., 1998). This unexpected result indicates that the situation is more complex than previously thought and is a particularly good example of the possible pitfalls of using in vitro experimental approaches to investigate complex processes such as fertilization.

In addition to the issues raised, the number of candidate proteins may also be a factor of the variety of approaches that researchers have used in investigations or differences in sample preparation (for example, in capacitation and the acrosomal status of the spermatozoa). The challenge remains to identify conclusively key sperm proteins and to characterize the important related processes, such as induction of acrosomal exocytosis, at the molecular level. In future, it will be necessary to reconstruct knowledge of individual molecular events back into the whole system to understand more fully the overall sequence of events during sperm–zona interaction.

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